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Review

Biological and environmental predictors of heterogeneity in neurocognitive ageing
Evidence from *Betula* and other longitudinal studies

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ABSTRACT

Individual differences in cognitive performance increase with advancing age, reflecting marked cognitive changes in some individuals along with little or no change in others. Genetic and lifestyle factors are assumed to influence cognitive performance in ageing by affecting the magnitude and extent of age-related brain changes (i.e., brain maintenance or atrophy), as well as the ability to recruit compensatory processes. The purpose of this review is to present findings from the Betula study and other longitudinal studies, with a focus on clarifying the role of key biological and environmental factors assumed to underlie individual differences in brain and cognitive ageing. We discuss the vital importance of sampling, analytic methods, consideration of non-ignorable dropout, and related issues for valid conclusions on factors that influence healthy neurocognitive ageing.

1. Introduction

Ageing research is increasingly abandoning universal descriptions of how functions and abilities are changing with advancing age. While not a new insight, as illustrated by publications in the mid 1900's (e.g., Havighurst, 1961; Havighurst and Albrecht, 1953; Katz, 1963) and later reinforced in a landmark paper by Rowe and Kahn, 1987 (see also Rowe and Kahn, 2015), there is now an emerging consensus on the existence of vast heterogeneity in the older population. This holds true for diverse domains such as engagement with life, risk for diseases, mental health, and physical activity. In the current review we focus on cognition, which is a key domain in many models and empirical studies of functional heterogeneity in ageing (Depp and Jeste, 2006).

Numerous studies in the field of cognitive ageing show that some

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cognitive functions, such as episodic long-term memory, are more age sensitive than others. It is also well established that individual differences in cognitive performance become magnified with advancing age (see Lindenberger, 2014). This magnification reflects different rates of change among individuals. Thus, while the rank order across individuals tends to be largely preserved from childhood to older age (Deary et al., 2004), the performance range is increased as some individuals show little or no change while others display marked change.

Brain maintenance, compensation, and *cognitive reserve* have been put forward as three interactive mechanisms that account for inter-individual variability in cognitive ageing (Fig. 1, Cabeza et al., 2018; Nyberg and Pudas, 2019; Stern et al., 2018). The theory of brain maintenance predicts that older individuals with a well-preserved ("youth-like") brain will also have well-preserved cognition (Nyberg et al., 2012). While brain maintenance is an advantageous prospect, the majority of the older population are expected to undergo age-related brain atrophy (e.g., Fjell et al., 2013). Still, some might perform well on cognitive tasks by utilizing compensatory processes (cf., Park and Reuter-Lorenz, 2009). Here, in the context of heterogeneity, it is important to stress that individuals are assumed to differ with regard to how likely they are to utilize compensation and also with regard to its effectiveness. A factor that has been introduced to explain such inter-individual variability in the ability to compensate is *cognitive reserve* (e.g., Stern, 2012). Thus, theoretically, if two older individuals present with exactly the same amount of cerebral changes, one may display better cognition due to higher cognitive reserve and more effective compensation. Marked age-related atrophy along with poor compensatory ability is indicative of pathological cognitive decline (Nyberg and Pudas, 2019), as such individuals are likely to meet criteria for mild cognitive impairment (MCI; e.g., Winblad et al., 2004) or mild neurocognitive disorder (Sachdev et al., 2014) and thus be on a path to various forms of dementia/major neurocognitive disorders.

A broad classification of factors that may contribute to heterogeneity in cognition in ageing is into biological (e.g., genetic) factors on one hand, and environmental (e.g., lifestyle) factors on the other hand. As illustrated in Fig. 1, these two classes of factors are assumed to exert their influence on cognitive performance in ageing by affecting the magnitude and extent of age-related brain changes (i.e., brain maintenance or atrophy), as well as the ability to utilize compensation. For example, genetic variation such as being an *APOE* ε4-carrier has been linked to increased risk for hippocampal atrophy in ageing (Cacciaglia et al., 2018), and low education levels have been related to low cognitive reserve and diminished ability to compensate (Stern, 2009). It should be stressed that while the classification of factors into biological or environmental is useful in many instances, some factors are hard to uniquely assign to one or the other category (e.g., personality; obesity). Moreover, as indicated by the bidirectional arrow in Fig. 1, biological and environmental factors can correlate and interact (e.g., a stronger impact of head injury on cognition in *APOE* ε4-carriers; Sundström et al., 2004; various forms of epigenetic effects, see e.g., Weinhold, 2006).

In general, the evidence for a causal role of certain genetic and lifestyle factors in accounting for heterogeneity in cognitive ageing is weak and indirect, and may in several cases suffer from the problem of *reverse causality* (e.g., an apparent association of reduced physical activity with developing a disease may in fact reflect an impact of the emerging disease on activity levels). Convincing evidence requires long time-series of data on diverse factors as genetics, lifestyle activities, and brain integrity. Moreover, ideally, the time-series should cover the life span, as some of the potentially relevant factors exert their influence early in life (Livingston et al., 2017; Walhovd et al., 2016).

In the following section, we will introduce the *Betula* longitudinal study of ageing, memory, and dementia. To the best of our knowledge this database is one of few to meet the above stated criteria for drawing strong conclusions on the relevance of certain factors for explaining heterogeneity in functioning in ageing. The Betula study has been described in a couple of past reviews (Nilsson et al., 1997, 2004). However, these are by now quite dated, and additional samples, test waves, and most critically additional domains such as brain imaging have been introduced after the publication of the prior reviews.

Next, selected findings from the Betula study will be discussed in relation to the model of cognitive heterogeneity in ageing that is outlined in Fig. 1. The model aligns well with the overall core aims of the Betula project: (i) study how memory and health develop across the adult lifespan, (ii) identify early cognitive signs and biological markers of dementia, and (iii) determine factors underlying successful ageing. In many instances, relevant evidence from other longitudinal studies will also be considered. In a final section we outline some outstanding issues for future research, including the composition of longitudinal study samples, harmonization and pooling of data from multiple databases, and longitudinal statistical analyses and treatment of nonignorable study dropout.

2. The Betula database – an overview

Three test waves were reported in the latest review of the Betula project (Nilsson et al., 2004). By now, some of the individuals have participated up to 7 times over 30 years. Most of the original test battery remains intact, but several additions have been made as summarized below.

2.1. Design

The study design adopted the basic principles of the general model proposed by Schaie (1965; 1986). This design aimed at overcoming some of the pitfalls in cross-sectional and longitudinal studies in the study of developmental problems. For example, while cross-sectional studies suffer from an inherent confounding of age and cohort and are a poor basis for studying age change (Nilsson et al., 2009), standard longitudinal analyses may be biased by effect of repeated assessments (e.g., practice effects), selective attrition as well as historical (period--related) influences.

The logic behind the design is that the relative influence of the basic determinants of behaviour: age, period, and cohort may be disentangled to attain a more accurate description of trajectories of within-person change. More specifically, the overall design permits two of the three factors to vary in so-called sequential designs. For example, a cross-sequential design involves multiple groups that differ in terms of birth cohort (e.g. born 1929 vs. 1933 for a five-year difference in Samples 1

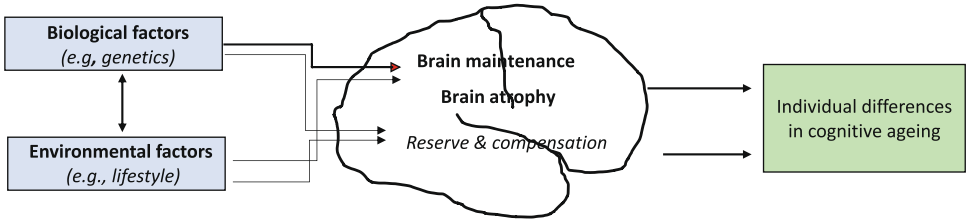

Fig. 1. Schematic model of how biological and environmental factors could influence cognitive performance in ageing by affecting the magnitude and extent of age-related brain changes (i.e., brain maintenance or atrophy), as well as the ability to recruit compensatory processes.

and 2) followed over time (e.g. five years), such that the cohort effect may be compared with the corresponding effect of ageing (i.e. change). To control for potential practice effects, at follow-up (W2) a new sample (S3), matched in cohort (and age) with the first sample (Table 1), is recruited and will, given adjustment for potential attrition effects serve as a basis for estimating retest effects (Rönnlund et al., 2005). Studies that adhere to such a sequential strategy (Rönnlund et al., 2005; Rönnlund and Nilsson, 2006a) confirmed that pure cross-sectional or longitudinal comparisons are sensitive to threats of the internal validity and that analyses based on the aforementioned principles provide a more accurate estimate of cognitive trajectories (for other examples of sequential analyses, see Schaie, 1965).

2.2. Participants and dropout

The Betula study participants, recruited from the city of Umeå on the northeast coast of Sweden (see Fig. 2) and its vicinity, were randomly sampled from the population registry, stratified by age and gender. The age cohorts were split into five-year intervals (25, 30, 35, … 80, 85, 95 yrs) and the number of males and females selected for inclusion was proportional to the male-female ratio in each age cohort of the general population. Participants who were demented, non-native Swedish speakers, had severe hearing/vision impairment, or congenital and acquired intellectual disabilities were excluded and accordingly replaced with another individual in the population registry of the same age and sex. The recruitment procedure has been extensively described (Nilsson et al., 1997, 2004).

The first wave of data collection started in 1988 and in total six main waves (W1-W6) of data collections have been completed, the sixth wave ended in 2014 (Fig. 2). In addition, a seventh test wave (W7) was carried out in 2017 for participants returning for a third neuroimaging (MRI/fMRI) follow-up and a limited set of health- and cognitive assessments. The study population originally comprised N = 4,445 individuals. However, at diagnostic follow-ups it was discovered that N = 19 (0.4%) had an ongoing dementia process at study inclusion and were consequently excluded from the final sample, as was one participant who withdrew study consent. Thus, the final Betula population comprises N = 4,425 (53.2% females) participants distributed over six cohorts (S1-S6), included at different waves and examined with five years interval up to six main waves (Table 1). During the course of the study N = 647 (14.6%) participants developed a dementia disorder and N = 3,464 (78.3%) remained non-demented. A number of participants (N = 314, 7.1%) could not be diagnostically evaluated (see Section 2.3 Dementia diagnostic assessments). In connection with the dementia diagnostic assessment in 2015-2017 mortality rates, N = 1,762 (39.8%), were also recorded.

The dropout frequencies are calculated for the longitudinal cohorts, viz. S1, S2, S3, S6. Cohorts S4 and S5 were not subject to follow-up and are thus not included in the numbers given below. There were several reasons for dropout where mortality N = 940 (45.7%) accounts for about half. The other reasons, accounting for the remaining dropout N = 1119 (54.3%), were (i) moved from the catchment area N = 114 (5.5%), and (ii) too ill or unwilling to participate or not re-invited to follow-up N = 1,005 (48.8 %). As for the latter, the default aim at the follow-up test waves was to invite and re-test as many participants as possible. However, some exceptions were made, which impacted on the return rates at: (I) W3, where only a part of the S2 cohort was re-invited due to insufficient funding; (II) W6, where a stop date for contacting and testing was set and priority was given to S1 and S3 participants and those of S6 included in the imaging-cohort (Fig. 2).

2.3. Dementia diagnostic assessments

2.3.1. Basis for assessment

The diagnostic assessment was aimed at ruling out dementia at study inclusion, identify incident dementia cases and disease onset year, and to dismiss individuals with non-progressive cognitive impairment. The diagnostic decision was based on long-term and detailed clinical data at a symptom and functional level obtained from multi-disciplinary written and electronic medical records. Thus, changes over time, could be followed individually, and other clinician's assessments and observations both before and after the disease onset could influence the final diagnosis.

In addition to the medical records, outcomes of the health- and memory assessments contributed to the diagnostic decision. As part of the protocol, a number of pre-defined criteria indicative of a possible state of current or forthcoming dementia were applied. The criteria were: (a) performance below 24 on the Mini-Mental State Examination (MMSE) and/or a decline with at least three points drop from the previous test occasion; (b) a decline from high to normal/low or from normal to low in cognitive performance compared to the previous test occasion. The high/low performance score was based on a composite cognitive measure, defined as a summed z-score of 1.8 above/below the mean of the age group (Nilsson et al., 1997); (c) self-reported memory dysfunction (d) behavioural or cognitive deviations suggestive of neurocognitive impairment. Participants exhibiting one or several of these criteria were considered at higher risk of dementia and accordingly carefully evaluated, primarily via medical records, and if deemed necessary referred for extended dementia evaluations. The diagnostic protocol did not systematically include post-mortem neuropathological examination nor CSF or neuroimaging biomarkers; however when available in the medical records from the diagnostic work in ordinary care, such findings were also taken into account. Most, if not all, individuals receiving a dementia diagnosis in Sweden have had at least one brain imaging investigation performed, most often a computed tomography brain scan.

2.3.2. Diagnostic criteria

In the Betula study, the same diagnostic criteria were applied throughout the study period (1988 - 2017). The information obtained

Table 1

The Betula study population. The table shows the number of performed health- (HT), memory- (MT) and MRI/fMRI (MR) examinations for cohorts S1 – S6 at test waves W1 – W6 and W7. #The neuroimaging (MRI/fMRI) numbers presented here are based on the longitudinal Imaging Ageing and Genetics (ImaGen) cohort. ## At W7, only participants from cohort S1 and S3 with imaging data at W5 and W6 were re-invited for a third MRI investigation and a limited set of health and cognitive assessments (for further details, see section 2.3.6 Brain imaging).

		W1		W2		W3		W4		W5			W6			W7##
		(1988-1991)		(1993-1995)		(1998-2001)		(2003-2005)		(2008-2010)			(2013-2014)			(2017)
Cohort	Age span at inclusion	HT	MT	HT	MT	HT	MT	HT	MT	HT	MT	MR#	HT	MT	MR#	MR#
S1	35-80 y	1000	1000	875	844	729	647	591	504	403	366	145	249	228	94	51
S2	35-80 y			994	994	673	610	-	-	-	-	-	-	-	-	-
S3	40-85 y			963	963	826	753	689	581	440	390	150	259	237	82	52
S4	35-90 y					553	552	-	-	-	-	-	-	-	-	-
S5	35-95 y							558	558	-	-	-	-	-	-	-
S6	25-80 y									357	357	81	66	65	55	-
	Total	1000	1000	2832	2801	2781	2562	1838	1643	1200	1113	376	574	530	231	103

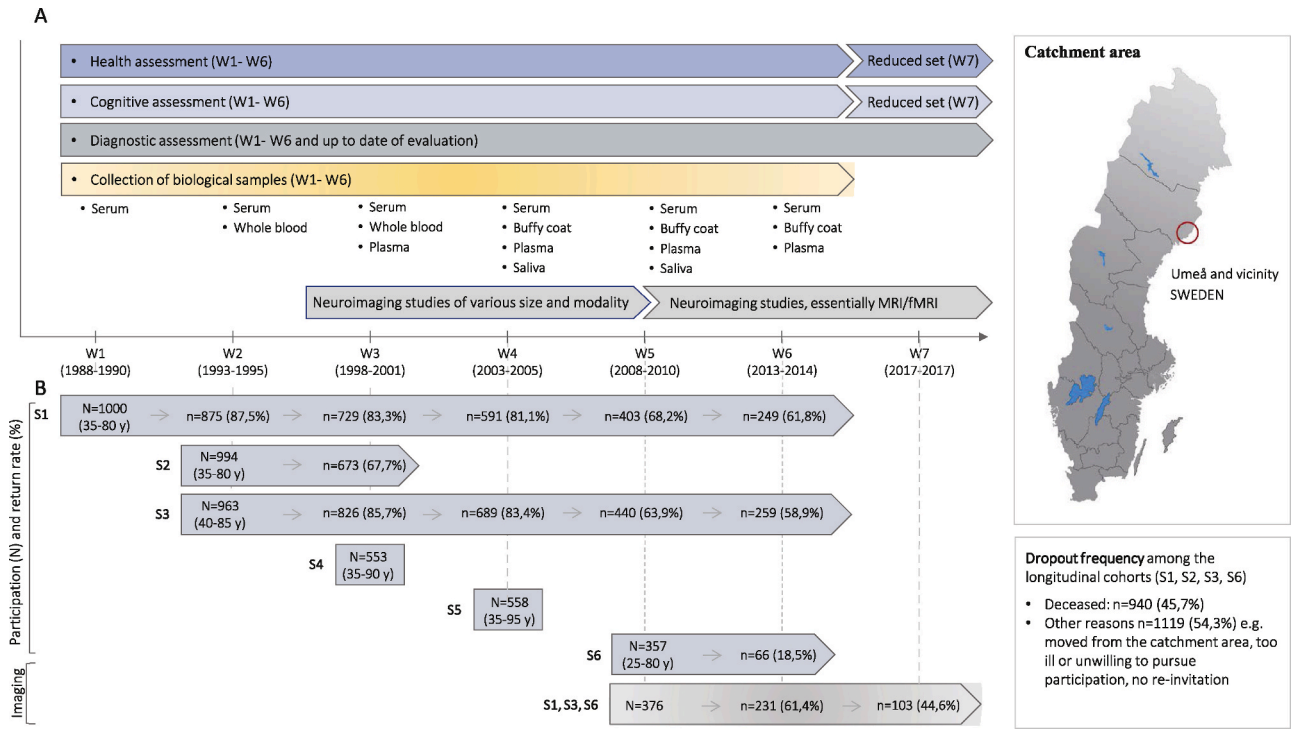

Fig. 2. Study participation and dropout. Panel A shows which assessments were carried out during the project. Panel B shows participation, baseline age span (y) and return rates (%) of each cohort at different test waves. The map of Sweden, with Umeå and vicinity in red circle, is modelled from an original by Statistics Sweden (www.scb.se).

was sufficient for applying clinical criteria-based systems, viz. the DSM-IV classification core criteria for dementia (American Psychiatric Association, 2000). Furthermore, also a number of in- and exclusion criteria were applied, shown to increase the sensitivity and specificity (Román et al., 1993; Wiederkehr et al., 2008a, 2008b). Participants receiving an Alzheimer's disease (AD) diagnosis showed an insidious onset and progressive cognitive decline as well as other symptoms typically attributable to clinical AD. Individuals with a cardiovascular burden accompanied with neurological signs, a fluctuating symptomatology, and stepwise progression of cognitive abilities received a clinical diagnosis of Vascular dementia (VaD). Cases with mixed features or scarce information were denoted Dementia not otherwise specified (Dementia NOS). Less common dementia disorders such as frontotemporal dementia (FTP), Parkinson dementia (PD), Lewy body dementia (LBD), cortico-basal syndrome (CBS) and progressive supranuclear palsy (PSP) were always extensively clinically examined and diagnosed within the healthcare system. Individuals with cognitive impairment close to death, often accompanied by severe somatic conditions and delirious episodes, were not considered having a dementia disorder, nor were individuals exhibiting non-progressive neurocognitive deficits after e.g. trauma, stroke, tumour, subarachnoid haemorrhage. The disease onset was defined as the year at which the clinical symptoms became sufficiently severe to interfere with social functioning and instrumental activities of daily living, i.e. when the core criteria of dementia were met (McKhann et al., 2011).

2.3.3. Measures to enhance diagnostic accuracy

At W1 and W3, all participants with suspect dementia were examined by two geropsychiatrists and clinical diagnoses were established through consensus. From test wave W4 and onwards, the diagnostic assessments were conducted solely by co-author R.A. To enhance diagnostic reliability, the diagnostic work-up every 5th year was performed blindly, i.e. without information on previously determined diagnostic status. The diagnosis obtained across the study period from W1 up to W4 was compared with W5 diagnostic data and disparities affecting diagnosis and/or age at onset were re-assessed and solved. In a similar fashion, a comparison was executed for the W5 and W6 diagnostic data.

In addition, individuals participating at W6 (N = 574) with inconsistent scores on the MMSE and clock test were identified and re-evaluated: i.e. non-demented individuals with MMSE $\leq$ 23 p and/or $\leq$2 p on the clock test and demented individuals with MMSE $\geq$ 27 p and/or $\geq$ 3 p at the clock test. The same procedure was applied for previous waves, however only including MMSE.

2.3.4. The dementia population

The final diagnostic evaluation, conducted in 2015-2017, showed that N = 647 (14.6%) of a total of 4 425 participants from cohorts S1-S6 had developed dementia, with a clear preponderance of AD (N = 346; 53.5%; whereof N = 341 of late onset AD, i.e. onset $\geq$ 65 yrs) and VaD (N = 227; 35.1%). The other dementia subtypes together constituted N = 74 (11.4%) of the demented population, with Dementia NOS (N = 28; 4.3%) and Parkinson dementia (N = 20; 3.1%) as the largest subgroups. None of the other subtypes (LBD, FTD, CBD, PSP, and alcohol-induced dementia) exceeded N = 15. No criteria-based MCI diagnoses were determined. At the time of evaluation N = 3,464 individuals (78.3%) remained non-demented. A proportion of the study population (N = 314; 7,1%) could for various reasons (moved from the catchment area, did not consent evaluation of medical records or had insufficient basis for assessment) not be diagnostically evaluated, i.e. were lost to diagnostic follow-up (Fig. 3). The distribution of disease onset ages, by dementia subtype and gender, are shown in Table 2. Information on *APOE* ε4 carriage is available for 86.6% (N = 3,832) of the main population. The highest frequency of ε4-carriers was found in the AD group = 49.7%, followed by VaD = 34.8% and other dementia subtypes = 31.9%, compared to non-demented = 26.1%.

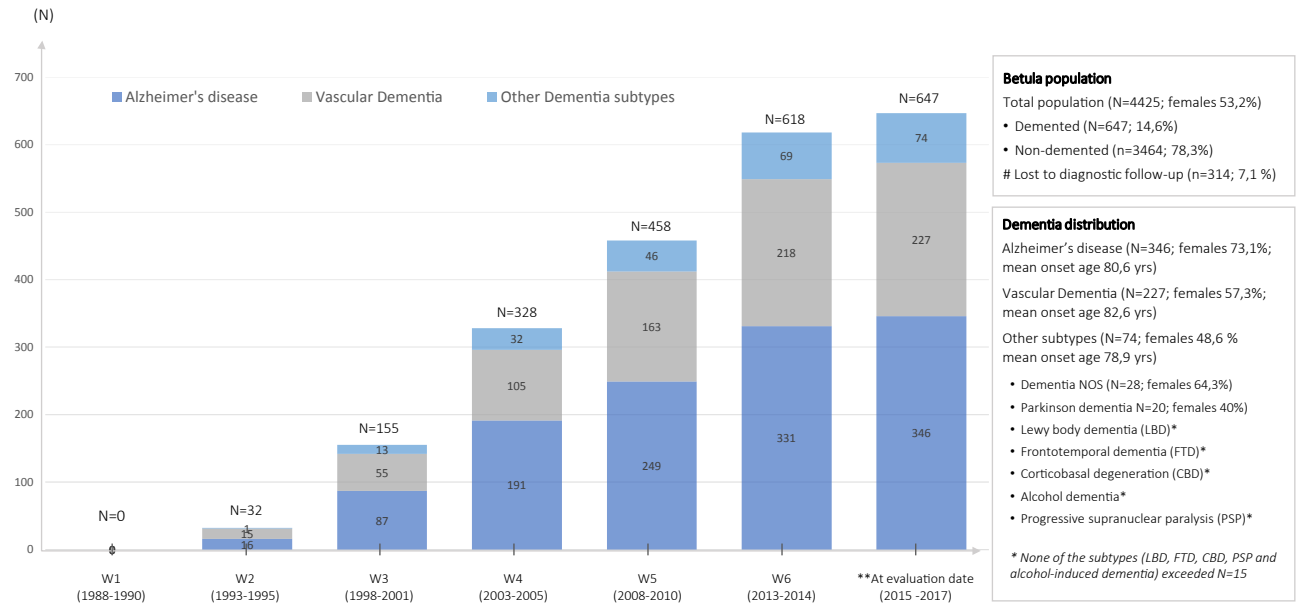

Fig. 3. Dementia cases in the Betula population. The figures comprise dementia cases (AD, VaD, Other subtypes) up to the mid-year of each test wave (W1-W5) and up to 2014 at W6. **At evaluation date corresponds to the time period (2015-2017) for which the most recent diagnostic assessments were carried out. # Individuals lost to diagnostic follow-up had either moved from the catchment area, did not consent evaluation of medical records or had insufficient basis for assessment.

Table 2
The table shows the number of dementia cases at the most recent diagnostic assessment conducted in 2015 – 2017. # Alzheimer's disease (AD): late onset (≥ 65 yrs): N=341; mean onset age 80,9 yrs; range 65 – 94 yrs Early onset (< 65 yrs): N=5; mean onset age 58,2 yrs; range 48 – 64 yrs. * Other dementia subtypes include: dementia not otherwise specified (Dementia NOS), frontotemporal dementia (FTP), Parkinson dementia (PD), Lewy body dementia (LBD), cortico-basal syndrome (CBS), progressive supranuclear palsy (PSP), and alcohol-induced dementia.

	Total dementia population N = 647		Female		Male	
	N	onset age mean; range	n (%)	onset age mean; range	n (%)	onset age mean; range
Alzheimer's disease (AD)#	346	80,6 (48 – 94)	253 (73,1)	80,5 (48 – 94)	93 (26,9)	80,8 (58 – 94)
Vascular dementia (VaD)	227	82,6 (66 – 98)	130 (57,3)	84,1 (66 – 98)	97 (42,7)	80,7 (66 – 93)
Other dementia subtypes *	74	78,9 (50 – 95)	36 (48,6)	81,0 (54 – 95)	38 (51,4)	76,9 (50 – 94)

2.3.5. Reflections on the diagnostic procedure

The clinical diagnostic approach applied in the Betula study paints a picture of the succession of symptoms at an individual level and allows various observations, including cognitive level/trajectories, to be weighted in the diagnostic decision. Commonly, the diagnostic picture becomes gradually clearer as the symptoms develop and more clinical observations are recorded. With the longitudinal study design, also the medical data recorded after diagnosis can be integrated into the diagnostic evaluation and contribute diagnostic accuracy. Notwithstanding, even though the richness of information allows possible/probable major subtypes of dementia with documented functional and cognitive decline to be defined, misclassifications can not be completely ruled out, and with no doubt, the diagnostic protocol would have benefitted from systematic integration of modern neuroradiological diagnostics and CSF biomarkers supporting the accuracy of the clinical diagnoses. However, it should be emphasized that such information was integrated when available in medical records. Recently analysed plasma-based biomarkers (T-tau, p-Tau, Aβ42/40, NFL) conducted within the frame of the study are available only for a small fraction of the study population (see Nyberg et al., 2020a) and hence not accounted for in the diagnostic work-up.

As the field moved to describe prodromal and clinical phases of AD based on biomarkers, a biomarker classification scheme would likely have a broad acceptance among clinicians and researchers and would probably disclose the neuropathophysiological heterogeneity known to exist in AD as well as contribute diagnostic accuracy and consensus. For VaD, the clinical diagnostic criteria have been debated over the years, resulting in a variety of criteria-based collections and even neuroimaging data reflects a large heterogeneity with regard to types and locations of cerebral lesions and its significance for dementia development (Debette et al., 2019).

The clinical diagnostic protocol did not include criteria-based MCI diagnoses, as available information was not sufficient for these diagnoses to be reliably established. However, a majority of participants with MCI will eventually develop dementia, and even though we acknowledge the concept, the MCI diagnosis itself is of less importance in our sample, as we could instead study those who have developed dementia and investigate factors present the years before their diagnosis. In that sense, we do study MCI individuals, and several publications have specifically focused on cognitive symptoms before dementia diagnosis (e.g. Josefsson et al., 2019; Rönnlund et al., 2015a; Boraxbekk et al., 2015).

As for the rather high disease mean onset age for AD, the onset age was defined as the year at which the core criteria of dementia were met. Consequently, this induces a higher mean onset age compared to defining the disease in the prodromal phase. Other factors that may contribute to the rather high onset age are that the cohorts, as per study design, were free of dementia at study inclusion and age stratified (an equal number of individuals from each 5-year age group), which entail individuals with an early onset of dementia to be systematically

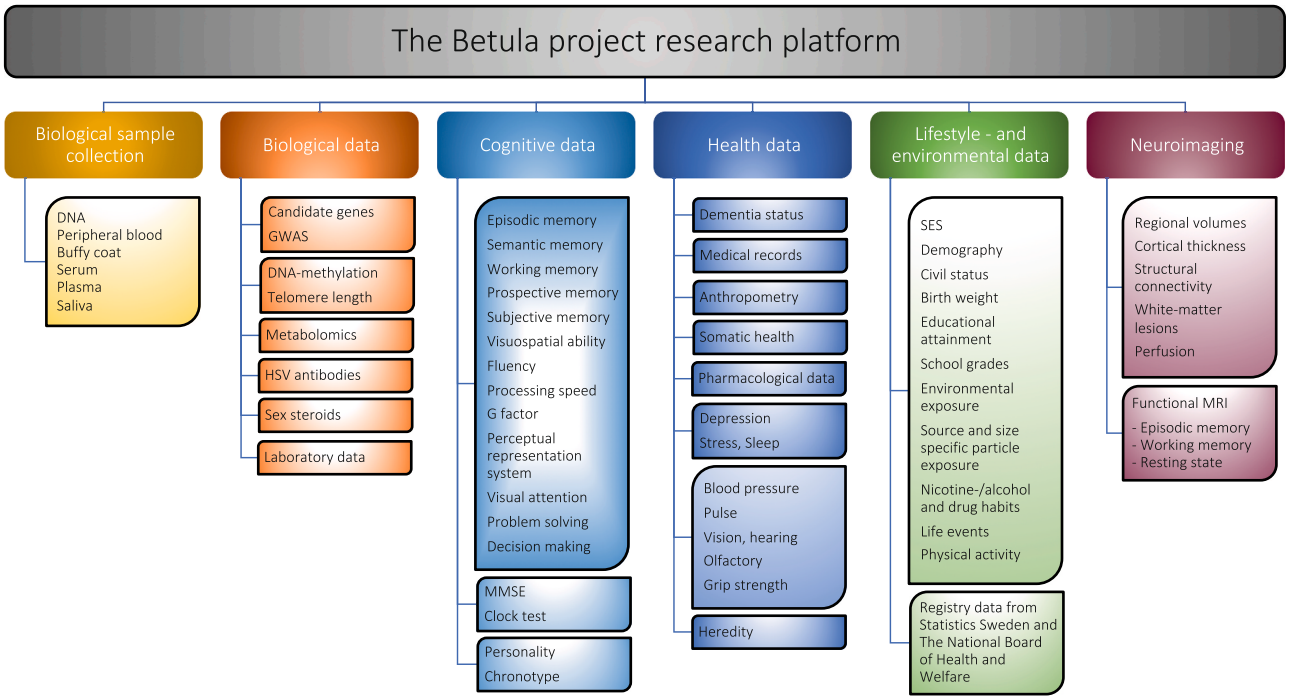

Fig. 4. Overview of the Betula database.

excluded and the study population to be somewhat skewed towards a higher age as compared to the underlying population. Furthermore, the mean onset age could also be influenced by that elderly cohorts accepting participation generally are cognitively healthier and more vigilant compared to those of the corresponding age declining participation.

Although different classification systems have been launched over the last decades and the availability of advanced diagnostic procedures like FDG-PET and CSF biomarkers gradually have increased, we have consistently applied the same diagnostic criteria throughout the study (1988-2017), which is important if one is to study changes over time.

2.4. Variables

A large number of variables have been repeatedly assessed in the Betula project, spanning the genetic, lifestyle, brain, and cognitive levels of the basic model in Fig. 1. An overview of the platform is presented in Fig. 4, and a brief description of selected variables is given below.

2.4.1. Biological sample collection and biological data

Blood sampling was systematically conducted as part of the Betula study. It was carried out at random over the day, from non-fasting subjects. Currently, the biological sample collection comprises serum (W1-W6), plasma (W3-W6), whole blood (W2-W3) and buffy coat (W4-W6), obtained from venous blood. From the majority of blood samples, DNA has been extracted to allow further genetic and epigenetic data collections. The sample collection was supplemented with saliva samples at waves W4 and W5 (Fig. 2). Sampling of cerebrospinal fluid (CSF) was not part of the study protocol.

The Betula data collection includes a broad set of biological variables. At each test wave (W1-W6), various health parameters were measured, see section 2.4.3 Health data. Clinical lab tests [e.g., Vitamin B12, folic acid, blood glucose, glycosylated haemoglobin, serum calcium levels, liver function tests, electrolytes (including Creatinine), complete blood count and differential white blood cell counts, thyroid function (T3, T4, TSH)] are available from W1 and/or W2. Blood glucose, haemoglobin and erythrocyte sedimentation rate were measured at each test wave. Morning urine samples, including e.g. u-glucose, u-leucocytes, u-erythrocytes, u-haemoglobin, u-albumin were measured at largely all test waves.

During the course of the study, various biological variables have been generated and added to the existing dataset. Imputed (1 K genome) Genome Wide Association (GWAS) data are available for (I) 1481 individuals from the longitudinal cohorts S1 and S3, genotyped at the Genotyping Platform of the Broad Institute of MIT and Harvard, and (II) 361 individuals of the neuroimaging sample, genotyped at the Department of Genomics, Life and Brain Center, University of Bonn. In total, 1,746 remained after quality control and account of overlap. Furthermore, a selection of candidate genes, implicated in e.g. Alzheimer's disease and neurocognitive function, was genotyped (i) The Apolipoprotein E (*APOE*) gene (ε2, ε3, ε4 alleles) are available in 2 990 participants from cohorts S1-S3 and S5 (see e.g., Sundström et al., 2004). Complementary phenotyping, distinguishing between *APOE* ε4-carriage or non-carriage, was conducted on 842 serum samples (S1-S6), adopting an ELISA-based method (Hemmingsson et al., submitted), (ii) The Catechol O-Methyltransferase (*COMT*) Val158Met polymorphism is available on 2824 individuals from S1-S3 and S5 (see Rönnlund et al., 2018), and the (iii) brain-derived neurotrophic factor (BDNF) val66met polymorphism is available on 2614 individuals from cohorts S1-S3 (see Olofsson et al., 2009).

Anti-HSV antibody status (HSV1/2 non-specific) data, obtained from serum and analyzed by enzyme-linked immunosorbent assays (ELISAs), are available for largely all participants aged $\geq$ 60 yrs (S1-S5) and in individuals $\leq$ 60 yrs (S1, S2, S5). Longitudinal analyzes were conducted on S1 and S3 participants, aged $\geq$60. Hence, 3432 participants contributed at least one serum sample, and 1231 contributed $\geq$ two samples from different test waves (Lövheim et al., 2015).

Leukocyte telomere length was measured on blood samples from the longitudinal cohorts S1 and S3. In total, 4093 analyses were conducted on 1751 unique individuals. In addition, longitudinal telomere length measures on cohort S6 are completed and quality control and normalization are currently underway. Relative telomere length (RTL) was determined by a quantitative-PCR method (Cawthon, 2002; Degerman et al., 2017; Norberg et al., 2018).

Longitudinal DNA methylation (DNAm) analyses (N = 235) were obtained for 113 individuals from S1 and S3 employing high density

arrays covering 485577 CpG sites (HumMeth450 K, Illumina, San Diego, USA), (see Degerman et al., 2014, 2017). The 353 CpG sites "epigenetic clock" prediction model by Horvath (2013) was used to determine the biological epigenetic (DNAm) age of each blood sample.

Blood-based biomarkers for neurodegeneration and amyloid deposition have been quantified in a longitudinal neuroimaging sample (N = 100) and in a cross-sectional case (AD)-control sample (N = 268). The analyses were performed at the Clinical Neurochemistry Laboratory, Sahlgrenska University, Sweden and included total Tau (T-tau); phosphorylated Tau (p-Tau) and amyloid-β; (Aβ42/40), and neurofilament light (NFL; Nyberg et al., 2020b). Other biological variables are e.g. biofluid metabolite profiles (Figueira et al., 2016; Figueira et al., 2019; Mousavi et al., 2014) and hormones (see e.g. Yonker et al., 2003, 2006). The blood-based hormone levels (total testosterone, albumin, SHBG, and estradiol) were analyzed for a subsample of participants at W2, and for all cohorts at W3. Analyses were carried out at the Clinical Chemistry Laboratory, Karolinska Hospital, Stockholm, and at the Department of Pharmacology, Göteborg University, Göteborg.

2.4.2. Cognitive data

The test battery (waves 1-6) aimed to cover theoretically motivated constructs, with a specific focus on memory and to capture multiple processes and hypothetical memory systems (Nilsson et al., 1997). Episodic memory was in particular focus, and in construction and choice of measures, efforts were to capture variations in the nature of the materials, including to-be-remembered materials (e.g., words, sentences, actions, and faces) and in means of assessment (free recall, cued recall, and recognition). Semantic memory was assessed using tasks that require rapid retrieval of information from memory (word fluency) and knowledge (e.g., vocabulary). Another measure included from the start was WAIS-R Block Design (Wechsler, 1981), typically considered as an indicator of spatial visualization ability and fluid cognition. Apart from the measures included from the start, measures of additional constructs, for example processing speed (Sternäng et al., 2008), working memory (Rönnlund et al., 2015b), and decision-making competence (Del Missier et al., 2013, 2020) were added (W 3-5).

Following psychometric evaluation of individual measures, a recommendation (Rönnlund and Nilsson, 2006b) was to combine individual measures or use a latent level approach to overcome shortcomings with regard to internal consistency of some of the individual tests. Nyberg (1994) demonstrated good fit for a latent-factor model distinguishing episodic and semantic memory, superior to that for a unitary model. Further differentiation and evidence of metric invariance across gender and time was established for these ability factors (e.g., Nyberg et al., 2003).

2.4.3. Health data

During the first test session of each test wave (W1-W6), a trained nurse conducted an extensive health examination and an interview regarding participant's health status, lasting approximately 1.5 to 2 hours in total. The nurse also administrated various health questionnaires and collected blood and urine samples for clinical laboratory analyses. Blood and saliva samples were also sampled and stored to enable biologically oriented research (cf., 2.3.1). The health examination included measurements such as height, weight, waist-hip ratio, blood pressure, pulse, vision, hearing, olfactory function/odour identification, triceps skinfold and grip strength. Participants were asked about their subjective health (e.g. back pain, stomache/gastrointenstinal problems, aching joints) and provided descriptions of prior and present diseases/conditions (e.g. heart disease, diabetes, high blood pressure). In addition, participants completed a number of established questionnaires related to their health, for example, questionnaires on sleep (Karolinska Sleep Questionnaire [KSQ]) (Nordin et al., 2013), stress (Perceived Stress Questionnaire [PSQ](Bergdahl and Bergdahl, 2002), depression (Center of Epidemiological Studies Depression Scale [CES-D]) (Lewinsohn et al., 1997) and a revised version of Katz activities of daily living (ADL) index (Katz et al., 1963; Hulter-Asberg, 1984).

2.4.4. Lifestyle- and environmental data

From W1 and onwards, lifestyle and environmental data were collected through questionnaires and personal interviews conducted by a trained nurse. These data include marital status, education, type of residence, presence of children (biological and adopted, living or dead), family history (number of siblings, etc.), living situation, work status, spouse's work status, environmental exposure (e.g., working with asbestos-containing material), critical life events, birth weight, complications at birth, and a number of lifestyle variables (e.g., smoking, alcohol, drug use). In addition, information about participants' participation in different leisure and physical activities (past and current) was collected as well as the quality and size of participants' social networks. From W5, additional questionnaires was included with regard to physical activity, which include measures of physical activity level (SGPALS; Saltin and Grimby, 1968), frequency of engagement in physical activity, activity levels compared to others, changes in physical activity pattern, and retrospective evaluation of level of physical activity earlier in life.

2.4.5. Data obtained from national registers and other external sources

In addition to the existing database of health, cognitive, lifestyle- and environmental variables, data were retrieved from national registers and a number of other external sources. The Swedish registry data obtained from the National Board of Health and Welfare include a broad range of health-related variables from the National Patient Register (in-patient care and outpatient doctor visits), the Swedish Cancer Register, the Death Cause Register, and the Swedish Prescribed Drug Register. The registry data acquired from Statistics Sweden comprise socioeconomic- and demographic variables from the Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), the Income and Taxation Register (IoT), and the Register of the Total Population (RTB). The data extend from each registers' start up to 2014, which in large corresponds to the time interval of the Betula study.

Two types of measures for early-life cognitive ability have been obtained. School grades were manually retrieved from archives for a subset of longitudinally followed participants (N = 727). Grades from six school subjects were extracted: mathematics, Swedish, history, biology, geography, and scripture knowledge. The majority of grade reports (95.5%) are from the sixth grade, approximately age 12 (see also Pudas and Rönnlund, 2019). Three cognitive tests from the Swedish Military Enlistment data, collected during the years 1954-1967, were retrieved for a subset of men at age 18 (N = 435). The tests were designed to measure inductive ability, word discrimination, and technical comprehension (Carlstedt, 2000). The tests were used as indicators of a general cognitive ability (g) factor, and this factor was found to be strongly associated with the corresponding g factor measured in the Betula project and also with working memory performance (Rönnlund et al., 2015).

Furthermore, estimates of annual mean levels of nitrogen oxides (NOx) at the participants' residential addresses (geocoded using information from the Swedish population registry) have been obtained for N = 2779 participants (S1-S3) participating at W2 (1993-1995). Exposure was assessed using a land-use regression (LUR) model with a spatial resolution of 50 m × 50 m. The model was built around multiple measuring sites spread throughout the studied area, and a 4-week long measurement was obtained between November 2009 and June 2010 with diffusive samplers (Ogawa samplers) to represent an annual average level of NO_x, a commonly used marker for long-term exposure to traffic-related air pollution (for details, see Oudin et al., 2016, 2019). Later, using similar methods, source-specific data on particles and soot in ambient air has been added (Oudin et al., 2018), as well as traffic-related noise (Andersson et al., 2018).

2.4.6. Brain imaging

Several neuroimaging studies have been conducted on Betula

subsamples, using SPECT (Elgh et al., 2002; Nyberg et al., 2009), PET (Mattsson et al., 2015), and structural and functional MRI (Lind et al., 2006; Nyberg et al., 2010; Söderlund et al., 2006). Here, we describe the largest and most recent one, conducted in 2009-2010 (N = 376, 52% female, age-range = 25-80 years), with longitudinal follow-ups in 2013-2014 (N = 231), and 2017 (N = 103). Participation was offered to all Betula participants from cohorts 1, 3, and 6 who had completed health and cognitive testing at W5, and who did not at that time-point self-report MRI contraindications, severe neurological disorders (e.g., stroke, neurosurgery), or visual/motor deficits that could interfere with fMRI data collection. Participant selection was stratified by age and gender, but blind to other characteristics. There was a slight selection effect among the scanned individuals, as their memory performance was on average 0.19 SDs above that of their parent samples at recruitment to the Betula study. This effect was more pronounced for the older age-cohorts, and mainly driven by selective attrition before W5. For the imaging participants, all variables in the core Betula database (Fig. 4) are available, and also later obtained data such as GWAS data and telomere length measures.

MRI acquisition was performed on the same General Electric 3 T scanner equipped with a 32-channel head coil at all time-points. At W5, the scanning session comprised a high-resolution anatomical T1-image, a T2 image, and a DTI sequence with 3 repetitions of 32 independent directions. In addition to a 6-minute resting state sequence (Salami et al., 2014), functional imaging encompassed a 10-minute episodic memory task containing encoding and cued recall of face-name pairs (Pudas et al., 2013), and a 10-minute Sternberg-type working memory task containing maintenance and manipulation of letter stimuli, as well as a low level control condition (Nyberg et al., 2014). The imaging sequences remained largely the same at W6, with the addition of a perfusion (arterial spin labelling) sequence (Boraxbekk et al., 2016). At W7 a novel 12-minute episodic-memory fMRI task (Nyberg et al., 2020) replaced the working memory fMRI task from W5/W6. This novel task involved recognition of fragmented, morphed or unaltered faces from the face-named task previously described, intended to tax pattern separation and completion processes.

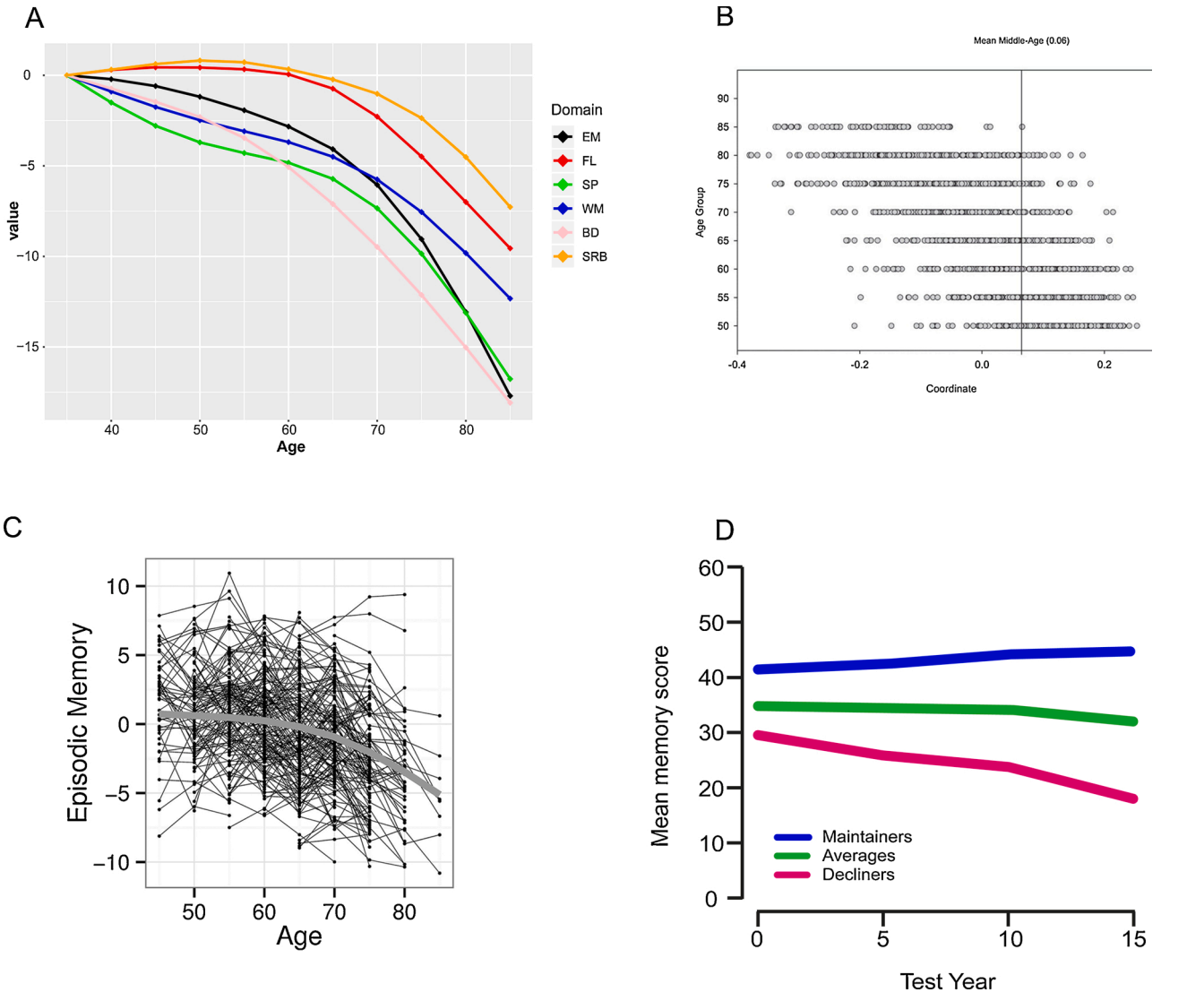

Fig. 5. Age-related cognitive decline and heterogeneity in the Betula study. (A) Average patterns of cognitive age trajectories for EM = episodic memory, FL = word fluency; SP = speed of processing, WM = working memory, BD = block design, SRB = vocabulary; (B) Individual differences in cognition as a function of age group (from Habib et al., 2007); (C) Spaghetti plot illustrating heterogeneity in episodic-memory change (from Gorbach et al., 2017); (D) Classification of the sample into individuals with average, faster declining, and maintained episodic performance in ageing (from Josefsson et al., 2012).

3. Individual differences in cognitive ageing

3.1. Average onset of cognitive change

Longitudinal studies estimate average onset of cognitive decline to occur considerably later than what estimates from cross-sectional designs suggest (see Rönnlund et al., 2005). For episodic memory, the average onset of longitudinal change is around age 60, whereas it occurs a bit earlier or later for other cognitive functions (Fig. 5A). The earliest onset of change is seen for speed-of-processing, which together with visuo-spatial functioning (block design) and episodic memory are the domains that show the greatest reduction in older age. Collectively, this change pattern across different cognitive functions in Betula (see e.g., Gorbach et al., 2017) replicates closely the longitudinal pattern seen in the Seattle Longitudinal Study (SLS; Schaie, 1994).

An age-related loss is also seen for several functions that are not standard cognitive measures. One example is olfactory function, where longitudinal findings from Betula show a robust decline in odour identification (Hedner et al., 2010). Another example is problem-solving as measured by the Tower of Hanoi puzzle, which also is an age-sensitive function as shown by age-related increases in number of moves, time to task completion, and rule violations (Rönnlund et al., 2001, 2008).

3.2. Cognitive heterogeneity

The population-based sampling in Betula allows us to paint a fairly representative picture of the vast heterogeneity that exist in cognitive functioning in the population. If inclusion instead is based on convenience sampling or restricted to individuals assessed at a memory clinic, a less representative sample and a more restricted range of score will most likely result. In a *Q-mode* factor analysis of 1463 individuals and 23 measures from the Betula cognitive battery, a common pattern of heterogeneity was observed across the cognitive measures (Fig. 5B; Habib et al., 2007). That is, both age-sensitive measures of episodic memory (e.g., recall) and less age-sensitive measures (e.g., vocabulary) contributed to this pattern. As can be seen in Fig. 5B, more participants from the older age groups fell in the lower (left) end of the distribution of scores, but a fair number of 70+ years individuals performed at or above the mean level for middle aged (50-65 years) participants. In a longitudinal follow-up five years later, 35% of the high-performing older adults continued to perform at a high level.

The findings from the Habib et al., 2007 study indicated that cognitive heterogeneity generalized across cognitive domains. Similarly, a recent large-scale meta-analysis of longitudinal change based on 22 unique datasets and over 30,000 individuals revealed that individual differences in longitudinal changes in diverse cognitive domains were moderately to strongly inter-correlated, and the shared variance in changes was found to increase with age (Tucker-Drob et al., 2019). Thus, an individual who showed little change in one cognitive domain was also likely to show little change in another age-sensitive domain, or no or even positive change in age-*in*sensitive domains such as semantic memory. These findings support a common factor structure of cognitive ageing, which may interact with more specific factors (cf., Deary et al., 2010).

At the specific level of episodic memory, analyses of a composite score based on several of the episodic tasks from the Betula battery revealed marked heterogeneity (Fig. 5C, Gorbach et al., 2017). Analyses of heterogeneity in longitudinal episodic memory change in a pattern-mixture model that considered the effect of attrition supported three distinct patterns of change (Fig. 5D, Josefsson et al., 2012). The largest group (about two-thirds of the sample of 1,558 participants) adhered to an average pattern of change, about 13% showed more accelerated decline, and 18% showed maintained memory over 15 years. Subsequent analyses showed that trajectories of episodic-memory

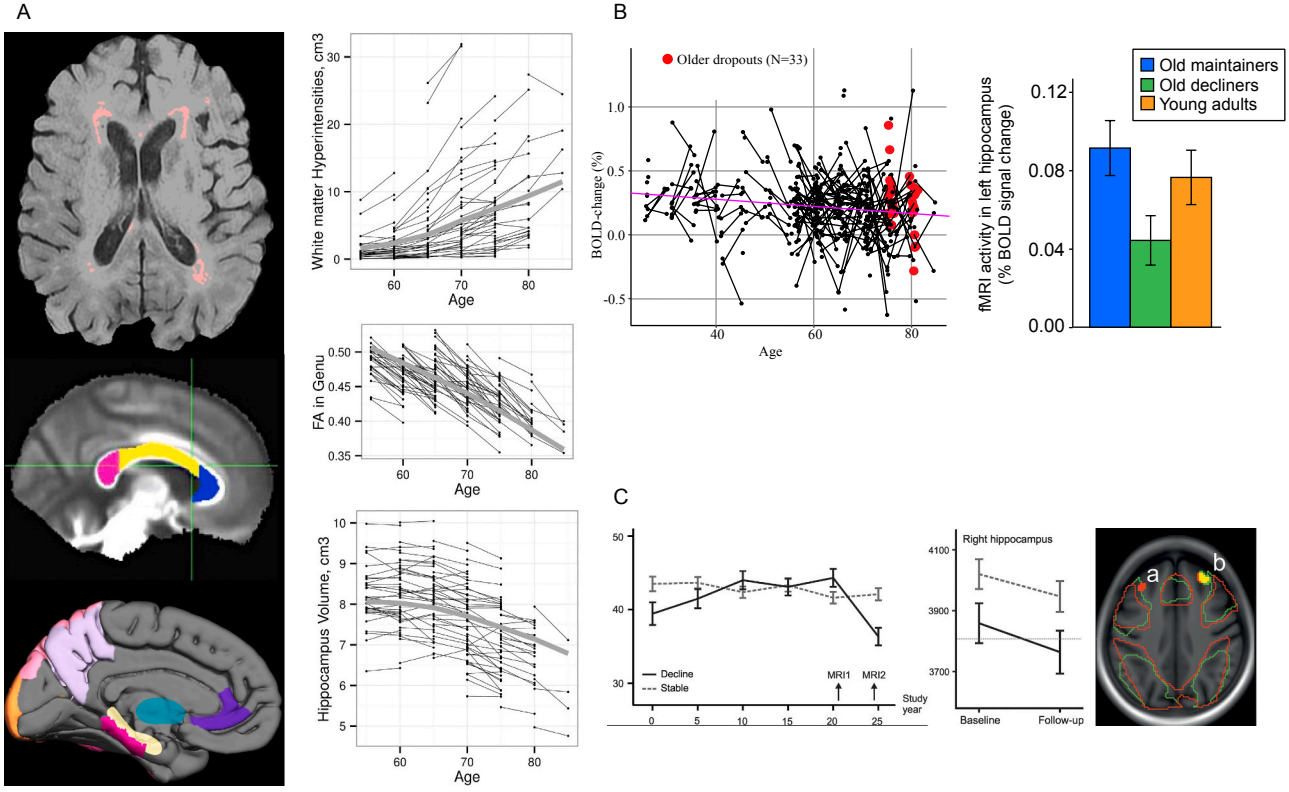

Fig. 6. Heterogeneity in brain ageing. (A) Illustration of individual differences in structural brain ageing (from Gorbach et al., 2017); (B) Illustration of heterogeneity in fMRI responses in the hippocampus, where red circles represent persons dropping out from the longitudinal follow-up (from Nyberg et al., 2019; Pudas et al., 2013); (C) Illustration of altered (compensatory) functional responses in the prefrontal cortex in relation to cognitive decline and hippocampus atrophy (from Pudas et al., 2018).

change strongly related to both upcoming vascular and Alzheimer's dementia (Josefsson et al., 2019).

Taken together, there is compelling evidence for marked heterogeneity in cognitive ageing (cf., Lindenberger, 2014). Next, we turn to the cerebral level of the model (Fig. 1).

4. Individual differences in structural and functional brain ageing

4.1. Brain maintenance

The brain-maintenance theory, which is a key component of the model displayed in Fig. 1, postulates (i) that older individuals differ widely in the amount of structural, functional, and neurochemical changes they display, and (ii) that there is a positive association between age-graded losses in brain and cognition (Nyberg et al., 2012). By now, evidence from several independent studies support the first assumption that there is marked heterogeneity in brain structure and function in ageing (see e.g., Nyberg, 2018; Nyberg and Lindenberger, 2020). This is illustrated in Fig. 6A using longitudinal Betula data (Gorbach et al., 2017). For white-matter lesions (hyperintensities), inter-hemispheric structural connectivity (white-matter microstructural integrity), and regional brain volumes (cortical and subcortical volumes) there are marked inter-individual differences in rates of structural brain ageing. The existence of marked heterogeneity in brain integrity in the older population is also captured by the concept of a "brain-age delta" (Franke et al., 2010). This delta represents the gap between the actual chronological age of individuals versus their brain age determined from one or several brain-imaging scans. Typically, there is a good but not perfect correspondence between chronological and brain age, such that some will have a positive delta indicating accelerated brain ageing whereas others will display a negative delta signaling a well-preserved brain (Nyberg and Wåhlin, 2020; for work on brain-age delta in Betula, see Dunås et al., submitted).

Longitudinal functional MRI has revealed marked heterogeneity in regional brain activity in ageing during task performance. In the associative face-name fMRI-task in Betula, the anterior hippocampus is particularly strongly recruited during memory encoding. This activation response decreases bilaterally as a function of advancing age, along with marked individual differences (Fig. 6B, left panel; Nyberg et al., 2019). In analyses that built on the classification in Fig. 5D of individuals into maintainers, average, or decliners it was found that older maintainers had as high hippocampus encoding-related activity as younger adults (Fig. 6B, right panel; Pudas et al., 2013). These findings indicate that one mechanism behind successful cognitive ageing is preservation of hippocampus function. Here it must be stressed that the level of hippocampus activation cannot in and of itself be used as a marker of brain and cognitive integrity. The red circles in Fig. 6B (left panel) represent older individuals who dropped out from longitudinal follow-up, often due to upcoming dementia or death, and had worse memory performance than their age-matched counterparts who remained in the study (Nyberg et al., 2019). Still the older drop-out group showed hyper-activation of the anterior hippocampus during memory encoding. Critically, the dropouts also showed abnormal (right) prefrontal activation during encoding and altered frontal-hippocampus functional connectivity, indicating that defective strategic top-down processes contributed to the hippocampus hyper-activity in the dropouts. Thus, at least for episodic memory, functional brain maintenance in ageing is expressed as effective hippocampus recruitment in the task-appropriate context of frontal (and likely also non-frontal) brain activity.

Turning to the second key assumption of the brain maintenance account, demonstrations of longitudinal change-change brain-cognition relations are quite scarce. For episodic memory a significant relation has been observed with hippocampal atrophy. In a 1.5 T MRI study, intra-individual structural and functional brain changes were related to 10-years longitudinal change in episodic memory (Persson et al., 2012). It was found that individuals with declining memory performance had reduced hippocampus volume and functional activity. In another Betula study, 15-year cognitive changes were related to 4-5 years changes in 3 T MRI-derived measures of brain structure, with the most robust change-change relation seen for episodic memory and hippocampus volume (Gorbach et al., 2017). Together, these longitudinal findings provide converging support that the hippocampus is one critical brain node in the model in Fig. 1, in particular for individual differences in episodic-memory ageing.

For functional activation changes, analyses of resting-state connectivity have revealed reduced within-network connectivity in older age (Biswal et al., 2010; for a review, see Ferreira and Busatto, 2013), often along with increases in between-network connectivity (Chan et al., 2014). Intriguingly, while reduced functional connectivity in ageing has been seen for the default-mode network (DMN), elevated resting-state connectivity was observed in the hippocampal subsystem in a cross-sectional analysis of Betula data (Salami et al., 2014). This elevation in hippocampus connectivity at rest was confirmed in a longitudinal follow-up study (Salami et al., 2016). Specifically, while reduced functional connectivity was seen in the anterior hippocampus, there was an increase in functional connectivity for the right and left posterior hippocampus along with a reduction in hippocampal-cortical connectivity. Critically, a significant change-change relation was found, such that a greater elevation in ageing of posterior hippocampus connectivity was related to greater episodic-memory decline.

Recent analyses from the Betula project also link longitudinal changes in task-induced activity to cognitive decline, suggesting that maintaining a youth-like prefrontal task signature relates to preserved episodic memory in ageing (Johansson et al., 2020). Early imaging findings revealed that the left prefrontal cortex is more strongly engaged than the right during episodic-memory encoding whereas the opposite pattern is seen during retrieval, which formed the basis for the Hemispheric Encoding/Retrieval Asymmetry (HERA) model (Nyberg et al., 1996; Tulving et al., 1994). Data from the three large-scale imaging waves in Betula showed a consistent HERA pattern, and also that the HERA pattern longitudinally diminished with ageing (Johansson et al., 2020). The age-related decline in HERA was related to a decline in episodic memory, suggesting that the ability to dynamically bias hippocampus processing to encoding (pattern separation) or retrieval (pattern completion) via top-down signals from the prefrontal cortex is a key aspect of preserved episodic-memory functioning in ageing (cf., Nyberg et al., 2019). These fMRI findings support the second key assumption of the brain maintenance account.

4.2. Compensation and Cognitive Reserve

The prospect of attaining a high level of cognitive performance, despite cerebral age-related changes, by means of compensatory processes has attracted much interest. In particular, atypical recruitment of prefrontal regions in ageing has been observed in many studies starting with a study by Cabeza et al. (1997; see also Backman et al., 1999), and this activation pattern has been considered a possible neural correlate of compensation (see Cabeza, 2002; Cabeza et al., 2018). This position is well captured by a quote from the 2009 review by Park and Reuter-Lorenz; "pervasive increased frontal activation with age is a marker of an adaptive brain that engages in compensatory scaffolding in response to the challenges posed by declining neural structures and function" (p. 173).

In Betula, findings consistent with a compensatory prefrontal response have been observed. Persson et al. (2006) found that older adults with a declining memory performance over time (N = 20) had a smaller hippocampus volume than older individuals with maintained memory performance (N = 20), but stronger right frontal activity during an incidental episodic encoding task. Similarly, Salami et al. (2012) reported a multivariate analysis of cross-sectional data from the first large-scale data collection with the face-name fMRI task (N = 376). Two

significant network patterns were observed with the first reflecting a process-general encoding-retrieval network with a strong fronto-parietal contribution, and the second a dissociation between encoding and retrieval networks with the anterior hippocampus strongly linked to encoding. A median-split analysis separated participants older than 60 years into a subgroup (N = 90) with effective recruitment of the process-specific network and a subgroup (N = 91) who more weakly engaged the same network. Crucially, the process-general (frontal) network was more strongly engaged by the older adults who did not effectively recruit the hippocampus encoding network.

These imaging findings partly support the compensation view as formulated by Park and Reuter-Lorenz (2009) by showing higher prefrontal activation in older adults with declining brain structure and memory function. However, despite the upregulated frontal activity, reduced memory performance was seen, suggesting limited behavioral effectiveness of neural compensation. It should also be noted that relatively higher prefrontal functional responses have also been seen in high-performing older adults, which was interpreted to reflect functional reorganization to counteract age-related decline (Cabeza, 2002). Moreover, Pudas et al., 2013 suggested that higher prefrontal functional responses in maintainers could reflect stable individual differences present from younger age, possibly reflecting higher cognitive (cf., Stern, 2009) or brain (Katzman, 1993) reserve.

Taken together, higher frontal functional responses in older than younger age have been interpreted to reflect (i) compensation in response to age-related losses in brain structure and function, (ii) functional reorganization to counteract age-related decline, and (iii) stable individual differences that characterize cognitively high-performing elderly. In principle, all of these interpretations could be correct, for example reflecting functional heterogeneity among subregions of the prefrontal cortex. However, addressing the validity of the different accounts requires longitudinal data, as underscored by demonstrations that imaging data (just like memory data; Rönnlund et al., 2005) from cross-sectional versus longitudinal designs can support very different interpretations (Nyberg et al., 2010). Longitudinal support for the notion of stability in individual differences was obtained in a study showing that cognitive ability in midlife predicted functional brain activity up to 20 years later in a sample of 203 55-80 years old Betula participants (Pudas et al., 2014; for related findings on brain structure, see Karama et al., 2014). Thus, while not assessing overlap in fMRI signal over 20 years, these findings show that those older adults who had higher activity in episodic-memory task-relevant regions also had been high-performing on episodic tasks in midlife.

In another study by Pudas et al., 2018, individuals were classified as having stable or declining memory performance between two imaging sessions separated by 4-5 years (Fig. 6C, left panel). Prior to the first MRI session, the two groups had comparable stable performance levels. Both groups showed age-related hippocampus atrophy, but the declining group had a significantly smaller right hippocampus (Fig. 6C, middle panel). Critically, while no group differences in fMRI activity was seen at the first MRI session, the memory decliners showed elevated PFC responses at the second session relative their own level at the first session and relative to the stable group (Fig. 6C, right panel). The regions in which upregulated activity was observed were located near the borders of the core encoding (green contours) and retrieval (red contours) networks, suggesting that compensatory responses might be expressed outside task-relevant networks (cf., Düzel et al., 2011).

In sum, Betula findings are consistent with the model in Fig. 1. Admittedly, though, we have found little direct longitudinal evidence for well-preserved cognition through compensation for cerebral changes by utilizing a cognitive reserve. Indeed, it remains challenging to identify individuals who employ successful neural compensation as effectively that they withstand cognitive decline. A signature of such individuals could be structural brain atrophy in conjunction with elevated functional brain activity along with intact cognition. Awaiting such future studies, the following discussion of biological and environmental predictors will primarily concern the continuous dimensions of well-maintained brain integrity versus brain atrophy/altered functional networks, and correspondingly well-maintained cognition versus age-related cognitive impairment.

5. 'Biological' predictors of Individual differences in brain and cognitive ageing

5.1. Genetic factors

Cognitive ability is strongly influenced by genetics across the lifespan, with twin-based heritability estimates of 50-80% (McClearn et al., 1997; Reynolds and Finkel, 2015). Longitudinal age-related cognitive change is also substantially heritable (Finkel and Pedersen, 2004; Reynolds and Finkel, 2015). Although complex traits are highly polygenic with typically small effects of individual genes, a few candidate genes have consistently been linked to cognitive ageing, the most important one being the apolipoprotein E (*APOE*) ε4 allele, which also is the single strongest genetic risk factor for sporadic and late-onset AD (LOAD), increasing the risk up to 90% for ε4 homozygous compared to ε4 non-carriers (Corder et al., 1993; Farrer, 1997). AD is a multifactorial disease, and non-genetic risk factors, e.g. cardiovascular diseases, smoking, diabetes, lack of physical activity, social isolation, depression, dietary pattern and alcohol consumption as well as gene x life-style interactions have been identified (Livingston et al., 2017; Peters et al., 2019a). In the Rotterdam population study (N=6,352; follow-up 14.1 years), the interplay between genetic and life-style factors on the long-term risk of developing dementia was studied. *APOE* ε4 carriers most often had a younger disease onset, parental history of dementia, and higher total cholesterol levels. A favourable life-style profile could not compensate for a high *APOE*-risk, but avoiding an unhealthy life-style could potentially prevent or postpone the onset of dementia in those with a low to intermediate *APOE* genetic risk (Licher et al., 2019).

The design of the Betula project makes it possible to study the net effects of *APOE* on age- and dementia-associated cognitive change, adopting both cross-sectional and longitudinal data. In an early Betula study, cross-sectional comparisons stratified by age revealed no significant differences in episodic memory between carriers of the three *APOE* alleles (ε2, ε3, ε4). However, analyses of longitudinal data revealed a significant *APOE* ε4 effect on change of episodic memory, such that ε4-carriers lowered their performance more than non-carriers in tasks taxing on episodic memory. Furthermore, a dose effect was observed for ε4 carriers, in that homozygotes performed worse than heterozygotes, who in turn performed worse than ε4 non-carriers. This effect was demonstrated particularly in recall tasks, suggesting a deficit in encoding and retrieval in ε4 carriers (Nilsson et al., 2002). In an extended longitudinal data analysis using 23-28 years follow-up data (Josefsson et al., 2019), it was found that individuals who had a more rapid episodic-memory decline than age-average had a higher frequency of the *APOE* ε4 allele (50.7% vs. 28.7%), and more than a fourfold risk of developing dementia (AD and VaD), compared to those displaying an age-average decline. For individuals with a maintained episodic memory profile the *APOE* ε4 frequency was 25.8% and the risk of dementia was 2.6 times decreased, compared to those displaying an age-average decline. A more beneficial memory trajectory was also consistently associated with better outcome, in terms of later disease onset and age of death.

Studies on the Betula cohort investigated the effect of interaction between the *APOE* ε4 allele, health-, and lifestyle- factors. de Frias et al., 2007 examined the association between lipid levels, *APOE* ε4 carriership and longitudinal changes (10 years) in episodic memory. It was found that lipid levels moderated the influence of *APOE* on episodic memory such that among ε4-carriers, decline in recognition was more pronounced in individuals with higher cholesterol levels. Another example of *APOE* x environmental factor interaction was on participants with previous head injury, followed for five years, showing a five-fold higher

risk for developing dementia for e4-carriers, but not seen in non-carriers (Sundström et al., 2007b), see also section 5.5 Head injury. Recent cross-sectional and longitudinal results on the Betula population support an association between HSV carriage and episodic memory decline, particularly in *APOE* ε4 carriers (Lövheim et al., 2019), see also section 5.4 HSV and related markers.

Another single genetic polymorphism that has consistently been linked to cognitive ageing is a common valine to methionine amino-acid substitution (Val158Met) in the catechol O-methyltransferase (*COMT*) gene. The Val allele is associated with higher *COMT* enzymatic activity and consequently lower prefrontal dopamine availability relative to the Met allele. In Betula, the *COMT* 158Val allele has been associated to lower episodic memory performance in both middle age and old age (de Frias et al., 2004), and was less frequent among individuals that maintained a high level of episodic memory in ageing across 15 years, compared to individuals with average levels of age-related memory decline (Josefsson et al., 2012). In addition, greater memory decline observed in Val carriers was further magnified by increased pulse pressure (Persson et al., 2016). Using brain imaging, the number of Val alleles was linked to increased dorsolateral prefrontal cortex (DLPFC) activation during a low-demand task (working memory maintenance) and decreased DLPFC activation during a high-demand task (working memory manipulation). A similar pattern was seen in older compared to younger participants, suggesting that ageing and *COMT* Val impact DLPFC efficiency in a similar fashion via lower levels of synaptic dopamine in the PFC (Nyberg et al., 2014). There are also reports from other cohorts suggesting that the effect of *COMT* genotype on DLPCF efficiency is larger at older age (Sambataro et al., 2009) A third candidate gene for cognitive ageing is the brain-derived neurotrophic factor (*BDNF*). The Met66 allele has been linked to poorer memory and reduced hippocampal volume and activation (Kambeitz et al., 2012), and some studies report interaction effects of *BDNF* Val66Met and age (Hedner et al., 2010; Lindenberger, 2008; Sambataro et al., 2010), as well as a link to cognitive decline (Boots et al., 2017; Persson et al., 2013)

In a recent study on 2490 non-demented individuals from the population-based SNAC-K study, the individual and combined effects of the genetic variation of *APOE*, *BDNF, KIBRA*, and *CLSTN2* on level and change in different cognitive domains were estimated. The only significant single SNP association was that of *APOE* ε4 for perceptual speed and category fluency. None of the genes reached individually a statistically significant association for episodic memory. However, when combining the genes in a cumulative score, a greater number of disadvantageous alleles was associated with faster episodic memory decline. The effect remained significant also after excluding *APOE*, indicating that despite the dominant role of *APOE* as a genetic risk factor for dementia, *APOE* is less influent when it comes to predict cognitive decline in normal ageing (Laukka et al., 2020).

In contrast to candidate gene studies, genome-wide association studies (GWAS) have offered unbiased identification of genes related to diseases and traits, including cognitive ability (Davies et al., 2015, 2018), and brain structure (Hibar et al., 2015; Satizabal et al., 2019; van der Meer et al., 2018; van Erp et al., 2015) and a still growing number of additional genetic factors underlying late onset AD and related endophenotypes have been discovered (Kunkle et al., 2019; Marioni et al., 2018; Tan et al., 2019; Witoelar et al., 2018). In total, heritability for late-onset AD is about 60 % based on twin data (Gatz et al., 2006), and in the range of 25-63 % based on GWAS data (Anttila et al., 2018) and current genetic findings account for 31% of late onset AD heritability (Ridge et al., 2016).

A recent longitudinal study in Betula by Kauppi et al. (2020) utilized the polygenic score (PGS) approach by adopting two polygenic scores as predictors of cognitive level and change in healthy ageing (i) a polygenic risk score for AD based on IGAP data (Lambert et al., 2013) and (ii) a polygenic profile score for cognitive performance, based on a meta-analysis of COGENT (Trampush et al., 2017) and the UK Biobank (Lee et al., 2018). While PGS for cognitive ability was associated with cognitive level but not change (slope), the opposite was seen for PGS AD, i.e. an association with cognitive change but not level. The association remained significant also when estimates of cognitive slope was restricted to individuals that were confirmed to stay non-demented for a minimum of six years after the last time point for which cognitive slope was estimated. The results suggest that genetics of cognitive decline in clinically healthy elderly overlap more with genetics of AD than genes related to the level of cognitive ability. To what extent this reflects early pathological processes linked to subsequent AD or whether AD-related processes partly influence age-related cognitive decline in healthy individuals remains to be evaluated.

5.2. Telomere length and the epigenetic clock

The length of telomeres, the protective "end-caps" of chromosomes, is a well-studied biomarker for age-related diseases and mortality (Blackburn et al., 2015) that has also been linked to cognitive ageing, albeit inconsistently (Hägg et al., 2017; Zhan et al., 2018). In Betula, shorter baseline leukocyte telomere length (LTL) predicted more episodic-memory decline across an up to 20-year follow-up, but the rate of LTL change over time was not associated with the rate of memory decline (Pudas et al., submitted). The absence of change-change associations corroborates a previous longitudinal study (Harris et al., 2016). Thus, although short LTL, potentially established in early life, appears to be a predictive factor for cognitive ageing in Betula and some other studies (Devore et al., 2011; Yaffe et al., 2011), adulthood LTL shortening appears less informative of individual differences in cognitive ageing. Furthermore, shorter LTL was previously found to be associated with greater subcortical brain atrophy as well as white-matter hyperintensities in Betula (Wikgren et al., 2014, also see Staffaroni et al., 2018). Among certain genetic risk groups, associations might be reversed, with longer telomeres being associated with worse outcomes (Wikgren et al., 2012a, 2012b), but these early results await replication in larger samples.

DNA-methylation (DNAm) profiles, an epigenetic ageing biomarker, also showed associations with longitudinal 15-year memory trajectories in a small-scale Betula study (Degerman et al., 2017). DNAm profiles allow computation of epigenetic age acceleration or the "epigenetic clock", i.e., whether an individual is epigenetically older or younger than expected for their chronological age, which has been shown to predict several ageing outcomes and mortality (Hannum et al., 2013; Horvath, 2013). Degerman et al., 2017 found that individuals (N = 16) who had high maintained memory profiles across 15 years were estimated to be 3 years epigenetically younger than age-matched individuals with average or declining memory trajectories. This finding extends previous cross-sectional observations (Marioni et al., 2015), but also awaits replication in larger samples.

5.3. Sex differences

Several studies on the Betula samples have established sex differences in cognitive abilities, most prominently a female superiority in episodic memory and verbal production tasks, and a male advantage for spatial tasks (de Frias et al., 2006; Herlitz et al., 1997; Maitland et al., 2004; Yonker et al., 2005). In line with a meta-analysis on sex differences in episodic memory (Asperholm et al., 2019), results from cross-sectional analyses of Betula data (Maitland et al., 2004) indicate that the female advantage in episodic memory is smaller in advanced age as compared to middle-age. In contrast, longitudinal analyses of Betula data (de Frias et al., 2006) and data from the Berlin Aging Study (Gerstorf et al., 2006) report stable sex differences in episodic memory and visuospatial ability across 10 years of longitudinal follow-up, much in line with findings from a systematic review (Ferreira et al., 2014).

Although most longitudinal analyses seem to indicate similar magnitude of age-related cognitive decline for men and women, not all

do. A later Betula study used 15-20 years of longitudinal follow-up of episodic memory for a classification into cognitive maintainers, average performers and decliners, and female sex was found to be a predictor for membership in the maintainer group (Josefsson et al., 2012). The observation of lesser decline in women in clinically normal populations is in line with some longitudinal neuroimaging studies' reports of faster atrophy across several brain areas in men compared to women (Armstrong et al., 2019; Ritchie et al., 2015). However, other longitudinal neuroimaging studies largely fail to observe differential atrophy rates for females and males (Raz et al., 2005).

The cross-sectional findings suggesting slightly smaller sex differences late in life than in earlier periods of life (Asperholm et al., 2019; Maitland et al., 2004) could result from earlier cohorts of women being at an disadvantage in regard to living conditions and educational opportunities relative to men (Weber et al., 2014), rather than from sex differences in age-related decline. Taken together, although most studies seem to indicate similar age-related declines in men and women (Ferreira et al., 2014; de Frias et al., 2006; Gerstorf et al., 2006; Raz et al., 2005), not all studies do (Armstrong et al., 2019; Josefsson et al., 2012; Ritchie et al., 2015), indicating that further longitudinal behavioural and neuroimaging studies on this topic are needed.

5.4. HSV and related markers

Accumulating evidence suggest that Herpes simplex type 1 (HSV1) infection is associated with an increased risk of development of Alzheimer's disease (Itzhaki et al., 2016; Mangold and Szpara, 2019). Recent animal and 3D brain tissue culture studies show that low-grade HSV infection can produce a complete AD-like phenotype without any genetic modifications as in traditional AD models (e.g., 3xTg and 5XFAD mice) (Cairns et al., 2020; De Chiara et al., 2019). In Betula, reactivated HSV infection (measured as presence of anti-HSV IgM antibodies in baseline serum samples) was found to increase the risk of subsequent AD development (Lövheim et al., 2015). The combination of *APOE* ε4 carriership and HSV carriership was also found to greatly increase the risk of episodic memory decline (Lövheim et al., 2019). This potential interaction between a host genetic factor and HSV for AD risk had previously been suggested from animal studies but was first shown in a prospective epidemiological cohort in Betula, and later confirmed in two other epidemiological cohorts (Linard et al., 2020; Lopatko Lindman et al., 2019).

5.5. Head injury

Head injury or mild traumatic brain injury (mTBI) is one of the most common neurologic conditions and it has been estimated to affect more than 600 in every 100,000 people each year (Cassidy et al., 2004). In addition to reports of cognitive difficulties after mTBI, common experience symptoms include headache, nausea, vomiting, blurred vision, fatigue, and sleep problems (McCrea et al., 2009). For most people, these problems resolve within days or a few weeks, but some report prolonged symptoms (Cassidy et al., 2004). Despite intensive research, it has not been possible to determine why so much heterogeneity exists in outcomes following mTBI. But some factors have been suggested as predictors, such as age at injury, repeated injuries, and psychiatric illness (e.g., depression, posttraumatic stress disorder) (McCrea et al., 2009). In addition, the influence of genes, particular the *APOE* gene, has been explored in this context (Lawrence et al., 2015). One difficulty in examining outcomes following mTBI is that pre-injury data are usually not available, especially regarding cognitive performance. Sundström et al. (2004) examined pre- and post-injury performance in the Betula project and found that *APOE* ε4 carriers showed significant decreased post-injury performance on several cognitive tests, whereas non-carriers showed no significant change between pre- and post-injury tests. When comparing post-injury performance with age- and gender-matched controls, no significant differences appear, thereby suggesting the feasibility with prospectively collected data, especially when examining subtle changes, as is common after mTBI.

Additional research as part of the Betula project shows that carriers of the *APOE* ε4 allele, compared to non-carriers, more often report fatigue after mTBI (Sundström et al., 2007a) and also have an increased risk of dementia (Sundström et al., 2007b). Support for a more unfavorable outcome for *APOE* ε4 carriers was confirmed in subsequent research. For example, a study of college athletes who were ε4 carriers showed both greater neurocognitive variability compared to athletes without the e4 allele (Merritt et al., 2018), and more cognitive symptom post-concussion (Merritt and Arnett, 2016). However, research has also produced conflicting results, especially regarding mild traumatic injuries, with some studies suggesting that the ε4 allele only influences recovery among individuals with more severe head injuries (for a review, see Lawrence et al., 2015). Intensive research has also explored the relationship between other candidate genes and outcome following mTBI (Kurowski et al., 2017; McDevitt and Krynetskiy, 2017).

6. 'Environmental' predictors of individual differences in brain and cognitive ageing

6.1. Education and childhood school performance

More highly educated individuals typically perform better on cognitive tests, but it is extensively debated whether level of schooling also protects against age-related cognitive or brain losses. While some longitudinal studies have reported protective effects on longitudinal rates of cognitive decline (Zahodne et al., 2015), a recent meta-analysis (Seblova et al., 2020) did not reveal such an association. Studies on Betula data have yielded mixed results. One study (Berggren et al., 2018) observed no protective effects of higher education on rates of decline in visuospatial ability, episodic memory, or semantic knowledge in 1,700 Betula participants (see also Lövdén et al., 2004). Similarly, Rönnlund et al., 2017 did not find evidence for young-adulthood intelligence or eduation attenuating decline in general intelligence across 15-years in a subsample of men. In Sörman et al., 2018, years of schooling was associated with more rapid *decline* in episodic memory and verbal fluency over a 15-year period in a subsample aged ≥55 years at study baseline (N = 1157). In contrast, a subsequent study showed that both higher school performance at age 12 and later educational attainment were associated with less episodic-memory decline across an up to 25-year follow-up (Pudas and Rönnlund, 2019). However, this protective effect was observed only in later-born cohorts, who were also younger at study baseline (N = 301; 35-55 years). It was speculated that this could be due to differential protective effects on younger- vs. older-age cognitive losses, or generational differences in access to education (which was more limited for the older age-cohorts). To summarize; although a protective effect of education could potentially exist in certain historical, cultural, or socioeconomic contexts, the evidence for a general protective effect of education on cognitive decline is very limited. Furthermore, as indicated by significant prediction of future ageing-related memory decline by age 12 school performance (Pudas and Rönnlund, 2019), some of the observed protective effects ascribed to education in previous studies may be caused by pre-existing (e.g., heritable) individuals differences in cognitive ability.

Turning to brain ageing, several cross-sectional studies report associations between level of education and larger local or global brain volumes, and functional brain characteristics (Foubert-Samier et al., 2012; Nobis et al., 2019; Springer et al., 2005), which could tentatively indicate larger brain reserve. However, the evidence for education reducing longitudinal atrophy rates or accumulation of other brain pathologies is mostly lacking (Brayne et al., 2010; Jiang et al., 2014; Raz et al., 2005). Thus, education does not appear to promote brain maintenance.

6.2. Physical activity and related factors

It has been proposed that around a third of all Alzheimer's disease cases worldwide can be related to potentially modifiable risk factors including physical inactivity, smoking, midlife hypertension, midlife obesity and diabetes (Norton et al., 2014). Several longitudinal studies support that physical activity in particular may be related to neurocognitive ageing. For example, data from the Prospective Population study of Women (part of the Gothenburg H70 Birth Cohort Studies), with an impressive 44-years follow-up time, showed that physical activity in midlife was associated with a reduced risk of dementia (Najar et al., 2019). Further, in the English Longitudinal Study of Ageing (ELSA), it was observed that physical activity preserved memory and executive functions over a ten year follow-up period (Hamer et al., 2018). Moreover, after conducting a joint analysis of four longitudinal studies (Long Beach Longitudinal Study; the Seattle Longitudinal Study; the Victoria Longitudinal study; the Octogenarian Twins Study) Lindwall et al., 2012 proposed a consistent pattern of a positive association between time-specific changes in physical activity and time-specific changes in cognition across all four cohorts.

In Betula, findings are rather consistent with the view that modifiable factors are associated with cognitive ageing. For example, a negative relationship between blood glucose levels and episodic memory performance in middle-aged non-diabetic and non-demented women has been observed (Backeström et al., 2015). Further, there was an association between higher cortisol levels and smaller prefrontal cortex area in older men and women (Stomby et al., 2016). Measures of physical activity have also been related to cognitive trajectories and brain health in Betula studies. In Josefsson et al. (2012), a higher proportion of those reporting being physically active were categorized as cognitive maintainers. In Boraxbekk et al. (2016) it was shown how those that maintained a higher level of physical activity over a decade had increased connectivity in the age-sensitive default mode network (DMN) as well as larger posterior cingulate cortex (PCC) volume and higher PCC perfusion. Taking advantage of the multi-modal MR imaging and the longitudinal design of Betula, it provided a potential neural link between the association of the benefits of long-term exercise and delayed onset of dementia (c.f. Rovio et al., 2005). Recently, results from within-person analyses suggest that continued engagement in physical activity has cognitive benefits on both episodic memory and verbal fluency in old age. At the between person-level, however, physical activity was not related to changes in cognitive function (Stenling et al., 2020).

6.3. Socially and cognitively stimulating activities

Previous reviews suggest that engagement in socially and cognitively stimulating activities in adulthood and old age can reduce the risk of cognitive decline and dementia diseases (see e.g. Fratiglioni et al., 2004; Stern and Munn, 2010; Wang et al., 2012). Similarly, longitudinal analyses on the Betula sample have shown that high levels of engagement in various leisure activities (e.g. association work) as well as having a socially active lifestyle (e.g. visiting/visits of friends) in old age (≥65 years) are related to decreased risk of incident all-cause dementia and Alzheimer disease (Eriksson Sörman et al., 2014; Sörman et al., 2015). However, in neither of these studies have any factors altered the risk of all-cause dementia or Alzheimer's disease when near-onset dementias were removed from the analyses. Results may therefore suggest that cognitive stimulation through the factors included in the analyses only can produce protective short-term effects, or alternately that reduced activity rather is caused by the prodromal phase of dementia in which individuals tend to withdraw from an engaged lifestyle. Later studies (Sörman et al., 2018) have shown that leisure time activities such as book reading were related to higher levels of verbal fluency and episodic memory in old age. However, it was not related to cognitive change. Still, other studies have found being engaged in social leisure activities (Mousavi-Nasab et al., 2014) and having a large social network (Sörman et al., 2017a) can have beneficial long-term effects on cognitive functioning (up to ten years), both among middle-aged and older aged, and in episodic memory in particular. It should be noted though that cognitive status as well seems to predict future change in cognitive activity (Mousavi-Nasab et al., 2014), which stresses that associations between engagement in cognitive stimulating activities and cognitive functioning seem to be bidirectional.

Many hours during a day and across the lifetime is spent at work, and the role of cognitively stimulating activities (work complexity) at work might be beneficial. Such cognitive advantages have been found both for level and/or change in cognitive performance, as well as in terms of reduced risk of developing dementia (see Fisher et al., 2017 for a review). However, in the Betula sample, using up to 24 years of follow-up, no evidence was revealed that work complexity was associated with all-cause dementia or dementia subtypes (Sundström et al., 2020a). Moreover, history of occupational complexity has not been found to be related to 15-year cognitive change (episodic memory and verbal fluency) in old age (Sörman et al., submitted). Similarly, data from the Uppsala Birth Cohort Multigenerational Study and the Kungsholmen project, following individuals from 10 years of age, demonstrated that neither occupational complexity nor educational attainment were protective of dementia risk once the effect of early-life cognitive performance was taken into account (Dekhtyar et al., 2015; Dekhtyar et al., 2016).

Another brain training activity that has been of interest when we used the unique data from the Betula project is that of bilingualism. Speaking two or more language has repeatedly shown to stimulate cognitive ability in a positive manner (e.g., Bialystok et al., 2012, but see Lehtonen et al., 2018 for a meta-analysis regarding cross-sectional data). One of the first longitudinal investigations of a possible bilingual advantage in episodic memory was conducted by Ljungberg et al. (2013) by using data from the Betula study. The results showed that bilinguals outperformed monolinguals at baseline level and across time in both episodic memory (recall) and letter fluency. More recently, we concluded that this advantage might be influenced by the origin of the spoken languages (Ljungberg et al., 2020). The same bilingual advantage was later also found in executive processes that underpins performance in phonemic/letter fluency (Marsh et al., 2019), and also at baseline in dual-tasking. The latter however, did not hold longitudinally (Sörman et al., 2017b). Following up on findings on the possible protective effects of bilingualism on dementia (e.g., Craik et al., 2010), we followed cognitively intact monolinguals and bilinguals (≥60 years of age) for up to 10 years without noticing any reduced risk for bilingual participants to develop all-cause dementia or Alzheimer disease specifically (Ljungberg et al., 2016). We concluded both from this study and from the one of Ljungberg et al. (2013) and Sörman et al. (2017) that cognitive inactivity after retirement might confer detrimental effects.

6.4. Environmental factors and cognitive function

Evidence is increasing for air pollution to be risk factor for cognitive decline, Alzheimer's disease and other cognitive disorders, as stated in several literature reviews (Block and Calderón-Garcidueñas, 2009; Block et al., 2012; Clifford et al., 2016; Kilian and Kitazawa, 2018; Peters et al., 2019b; Power et al., 2016; Schikowski and Altuğ, 2020).

Inflammation and oxidative stress seem to be major pathways between exposure and cognitive decline (Oudin, 2020). More specifically, oxidative damage and increased presence of glial cells seem to be the cellular response to particulate air pollution exposure (Lopategui Cabezas et al., 2014; Dzamba et al., 2016). In line with this, exposure to air particulate matter in the brains of mice has been showed to provoke changes in inflammatory responses, an increase of beta-site APP cleaving enzyme expression and Aβ plaque, loss of dendritic spine density, reduced dendrite length in the hippocampus (CA1 region), as well as fewer amyloid precursor proteins (Bhatt et al., 2015; Fonken

et al., 2011). In the Betula study, there were clear associations between exposure to air pollution and dementia (Oudin et al., 2016; Oudin et al., 2018). However, long-term exposure to air pollution did not have any clear associations with episodic memory or episodic memory decline (Oudin et al., 2017), measured as a composite score previously used in the Betula study (Josefsson et al., 2012).

Given current evidence it is unlikely that the associations between air pollution exposure and cognitive function were to be explained by individual-level residual confounding (Power et al., 2016). However, other environmental factors, such as noise from traffic, railways or aircraft, or access to green space, may potentially confound the association between air pollution and cognitive function. Regarding noise (for example road traffic noise, railway noise, or aircraft noise), evidence for an association with cognitive function is more uncertain and less robust than for air pollution, and a greater number of studies are required (Clark and Paunovic, 2018). The pathway could be that chronic noise exposure dysregulates the neuroendocrine system, which may lead to hyperactivation of the sympathetic divisions of the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA)-axis, and increases stress hormones that affect brain and behaviour (Jafari et al., 2019). In the Betula study, exposure to noise from traffic did not seem to be a risk factor for dementia, or to influence the association between dementia and traffic-related air pollution previously observed (Andersson et al., 2018).

6.5. *Marital status, parental status, and loneliness*

Humans are social beings, and social relationships are central to our health and well-being (Holt-Lunstad et al., 2010). Research has suggested that social factors, such as marital status, are not only related to health and well-being, but also associated with cognitive performance and cognitive ageing. For example, Mousavi-Nasab et al. (2012) demonstrated that married persons in the Betula study performed better than single persons on episodic memory testsover a period of 5 years. In another Betula study, Sundström et al. (2014) examined both marital and parental status and found an elevated risk of dementia among widowed individuals and people without children, with particularly increased risk for widowed individuals who did not have children. Similar results were reported in a longitudinal study of the entire Swedish population, where each non-married subcategory was found to be associated with a significantly higher risk of dementia than the married group (Sundström et al., 2016).

Furthermore, some studies have focused on the absence of social belonging and, more specifically, on perceived loneliness, finding that loneliness was associated with diminished global cognitive function (Gow et al., 2013), executive function (Gilmour, 2011), immediate and delayed recall (Shankar et al., 2013), and reduced processing speed (Gilmour, 2011). Research also suggests that loneliness may be associated with increased risk of dementia. A recent Betula study (Sundström et al., 2020b) examined the subjective perceptions of feeling lonely on incident dementia. The results showed that loneliness was associated with significant increased risk of AD, but not with VaD. Adjustments for covariates, including depression, did not attenuate the relationship between loneliness and AD. The results from these studies underscore the importance of several aspects of social relationships when considering heterogeneity in cognitive ageing. Further research is needed to understand the possible causal nature of these associations.

7. Outlook: Challenges in the era of longitudinal neurocognitive studies

In this review we have highlighted the vital role of longitudinal evidence for characterizing heterogeneity in neurocognitive ageing and for identifying factors that contribute to such heterogeneity. Longitudinal findings suggest a later onset of average cognitive change than what is found in cross-sectional studies, which to a large degree reflects a confounding effect of cohort differences (e.g., in educational level) on the cross-sectional estimates (Rönnlund et al., 2005; cf., Schaie, 1994). Longitudinal studies also paint a more complex picture by showing that individuals with an above-average brain or cognitive score in older age may in fact have suffered quite some decline (e.g., from an above-average hippocampus volume in younger age; cf., Lupien et al., 2007). Conversely, low scores in some older individuals could well reflect stability in performance levels over time (for a related finding in the context of perceived stress, see Lindgren et al., 2016), but in the absence of longitudinal data such a low (cross-sectional) score might erroneously be interpreted as reflecting age-related decline.

The findings from Betula on factors that influence brain and cognitive ageing support many past conclusions from other longitudinal studies as discussed above, but challenge other conclusions that mainly were based on cross-sectional data (for example, the notion that well-preserved cognition can be achieved despite cerebral changes through compensatory processes supported by a cognitive reserve). Some of the factors that were considered are potentially modifiable (e.g., BMI, blood pressure, physical status, living conditions). From a practical perspective, such information is vital for recommendations on how individuals to some degree can influence their own neurocognitive ageing. It is critical that recommendations are based on solid evidence, preferably from longitudinal studies.

In this context it is gratifying to see that many longitudinal ageing/lifespan studies are ongoing, which promises additional novel findings on neurocognitive ageing in the near future. Some relevant examples include the Swedish NEAR (https://www.near-aging.se), the UK biobank (e.g., Folley et al., 2019); the Dallas Lifespan Brain Study (e.g., Rodrigue et al., 2012), the Harvard Aging Brain Study (e.g., Gatchel et al., 2019), the Seattle Longitudinal Study (e.g., Rast et al., 2018), the ENIGMA consortium (Thompson et al., 2014), and the European *Lifebrain* consortium (Walhovd et al., 2018). Betula are part of NEAR, ENIGMA, and Lifebrain, and also in the Psychiatric Genomics Consortium (PGC; e.g., Watson et al., 2020). The value of combining datasets to gain power is obvious for questions related to genetics as in the ENIGMA and PGC (where a part of the Betula population serves as controls), but also for detecting subtle influences of non-genetic factors. One example of the latter is a recent Lifebrain paper on the link between sleep and hippocampal atrophy (Fjell et al., 2020), an area of growing interest in the context of ageing and dementia.

We have advocated longitudinal studies in this review, but it is also critical to highlight that there are methodological issues that need to be considered for conclusions from longitudinal studies to be valid. We end this review by discussing some of these issues. A more extensive and general discussion is found in Nyberg et al., 2016.

7.1. *The representativeness of study samples*

All samples may be considered as coming from some larger population. However, for e.g. self-selected samples or convenience samples, the larger population they represent are usually quite narrow with respect to important characteristics such as age, education, socioeconomic status, etc. It is commonly recommended to define a large, general population from which study subjects are then sampled. For each subsample (S1-S6) in the Betula study, the respective samples are random population samples at their first test occasion and thus representative of the general population in the Umeå area at the respective sampling times. Indeed, comparisons between participants and the general population with regard to demographic factors at the time of study inclusion (e.g. education, income, marital status) have shown adequate population validity (Nilsson et al., 1997). During the course of a study as long as Betula, the representativeness of the original sample(-s) may be affected by several events. One important such event is dropout from the study, an issue important enough to warrant a separate section below. Another issue, inherent to any longitudinal study of considerable length, is that the population from which at least the earliest Betula samples were selected

is likely to differ from the corresponding population today, in terms of e.g. smoking and exercise habits. This relates to the well-known Flynn effect (Flynn 1984, 1987) which has indeed been examined within the Betula study (Rönnlund and Nilsson, 2009). We have worked rigorously to ensure that our results are valid for the population considered originally - but must also keep in mind to view those results in light of a changing population.

7.2. Statistical analyses and treatment of (nonignorable) study dropout

One of the biggest issues in longitudinal studies in general is dropout. Dropout may bias results and thus render them invalid for the population we set out to investigate. In this context the mechanism for dropout is an important tool. Broadly, dropout may be considered to depend on observed data only (ignorable dropout mechanism) or on both observed and unobserved data (nonignorable dropout mechanism). For exact technical definitions, see Little and Rubin (2002, pp. 117-120). While it is possible to investigate if dropout depends on observed data, there is no way of checking for non-ignorability using observed data. Non-ignorability is thus, by necessity, an assumption, although it is often deemed plausible (Glymour et al., 2012, Josefsson et al., 2012).

Assuming ignorable dropout, valid results are obtained using analysis methods that incorporate all of the observed data in the analysis, both from subjects completing all the follow-ups but also the data observed until dropout for those who do not complete. A well-known and often used option is to use so-called Mixed Models, either linear or generalized additive. Such models have been used frequently in Betula papers, one of the latest examples being Johansson et al. (2020). Another family of models yielding valid results under ignorable dropout are SEM/Latent change-models, which have been used to analyze Betula data by e.g. Rönnlund et al. (2017) and Pudas and Rönnlund (2019). If the dropout mechanism is assumed nonignorable, it is needed to specify a model for the dropout mechanism as well. Since no assumptions in such models are checkable using observed data, a common approach is to start out from the results obtained under the ignorability assumption, and then investigate several dropout models with respect to departure from the results under ignorability. Such sensitivity analyses may be performed in different manners, with common approaches being to use either selection models or pattern-mixture models (see e.g. Daniels and Hogan, 2008, chapters 8.3 and 8.4, respectively). In the Betula study, sensitivity analysis using selection models have been considered by Gorbach et al., 2017, and in the pattern-mixture approach (Josefsson et al., 2012, 2016) .

7.3. Harmonization and pooling of data from multiple longitudinal databases

Pooling data from many different studies/databases enables researchers to investigate a broader range of research questions with greater statistical power. These opportunities, however, come with some challenges, see Lesko et al. (2018) for an excellent overview on both opportunities and challenges. One question which does not seem to have an obvious answer is on what level data should be pooled – on the raw data level or results level (i.e. meta-analysis)? Relating back to Section 7.1, another important issue to consider is how the data collection design is specified in each study – is the sampling random from a population registry or self-selected? If the study populations are very heterogenous generalization may be difficult, but partially remedied by using meta-analysis instead of direct pooling of data since one can then estimate the between-study heterogeneity, see e.g. Higgins et al. (2003). There are also imaging specific issues, one of the most important being between-scanner variability. Such variability may be quite substantial, and variability within the same scanner before/after software upgrades may be on par with between-scanner variability (Han et al., 2006; Takao et al., 2013). Ideally, every pair of scanners within a larger collaborative project should have some subjects scanned on both scanners. We realize that it requires quite some planning and logistic considerations but may offer valuable information if realized (see Fjell et al., 2020).

7.4. Conclusion

Findings from Betula and other longitudinal studies are beginning to identify factors that account for the major individual differences that characterize neurocognitive ageing (Fig. 1). Some of these factors are modifiable (cf., Livingston et al., 2017), and interventions targeted at them can lead to maintained cognitive functioning (e.g., Ngandu et al., 2015). An increased understanding of how factors, such as vascular health (Wåhlin and Nyberg, 2019), promotes brain maintenance will support ageing individuals and societies to remain cognitively healthy.

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